We Claim:

1. A yeast cell comprising:

a) a nucleotide sequence encoding a first heterologous fusion protein comprising a first peptide of a peptide binding pair, or a segment thereof, joined to a transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising a second peptide of the binding pair, or a segment thereof, joined to a transcriptional activation protein transcriptional activation domain;

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein.

2. The yeast cell of claim 1 further comprising at least one endogenous nucleotide sequence selected from the group consisting of a nucleotide sequence encoding the transcriptional activation protein DNA binding domain, and a nucleotide sequence encoding the transcriptional activation protein transcriptional activation domain wherein at least one of the endogenous nucleotide sequences is inactivated by mutation or deletion.

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3. The yeast cell of claim 1 wherein the peptide binding pair comprises a ligand and a receptor to which the ligand binds.

4. The yeast cell of claim 1 wherein the transcriptional activation protein is Gal4, Gcn4, Hap1, Adr1, Swi5, Ste12, Mcm1, Yap1, Ace1, Ppr1, Arg81, Lac9, Qa1F, VP16, or a mammalian nuclear receptor.

5. The yeast cell of claim 1 wherein at least one of the heterologous fusion proteins is expressed from an autonomously-replicating plasmid.

6. The yeast cell of claim 5 wherein at least one peptide of the peptide binding pair is selected from the group consisting of a cytokine, an interleukin, a hematopoietic growth factor, insulin, an insulin-like growth factor, a growth hormone, prolactin, an interferon, a growth factor, a ligand for G-protein coupled receptors, a ligand for guanylyl cyclase receptors, a ligand for tyrosine phosphatase receptors, and a ligand for tyrosine kinase receptors.

7. The yeast cell of claim 6 wherein the peptide is a growth factor selected from the group consisting of epidermal growth factor, nerve growth factor, leukemia inhibitory factor, fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, tumor necrosis factor, oncostatin M, ciliary neurotrophic factor, erythropoietin, steel factor, placental lactogen, and TGF.

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8. The yeast cell of claim 1 wherein the DNA binding domain is a heterologous transcriptional activation protein DNA binding domain.

9. The yeast cell of claim 8 wherein the DNA binding protein is selected from the group consisting of a mammalian steroid receptor and bacterial LexA protein.

10. The yeast cell of claim 1 wherein the yeast cell is *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, or *Pichia pastoris*.

11. The yeast cell of claim 10 wherein the yeast cell is *Saccharomyces cerevisiae*.

12. The yeast cell of claim 1 wherein the luciferase gene is a *Renilla* luciferase gene.

13. The yeast cell of claim 1 wherein the luciferase gene is a *Photinus* luciferase gene.

14. The yeast cell of claim 1 wherein the first and second peptides of the peptide binding pair interact through extracellular interaction in their natural environment.

15. A yeast cell comprising:

a) a nucleotide sequence encoding a first heterologous fusion protein comprising a first peptide of a peptide binding pair, or a segment thereof, joined to a transcriptional activation protein DNA binding domain;

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b) a nucleotide sequence encoding a second heterologous fusion protein comprising a second peptide of the peptide binding pair, or a segment thereof, joined to a transcriptional activation protein transcriptional activation domain;

wherein the nucleotide sequence encoding either the first or second heterologous fusion protein is present in an effective copy number of at least 5 copies per yeast cell and the nucleotide sequence encoding the other heterologous fusion protein is present at a copy number of 1 or 2 per yeast cell;

and

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein, wherein expression of the luciferase gene prevents exhibition of a selected phenotype.

16. The yeast cell of claim 15 further comprising at least one endogenous nucleotide sequence selected from the group consisting of a nucleotide sequence encoding the transcriptional activation protein DNA binding domain, and a nucleotide sequence encoding the transcriptional activation protein transcriptonal activation domain wherein at least one of the endogenous

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nucleotide sequences is inactivated by reconstitution or deletion.

17. The yeast cell of claim 15 wherein the peptide binding pair comprises a ligand and a receptor for the ligand.

18. The yeast cell of claim 15 wherein the transcriptional activation protein is Gal4, Gcn4, Hap1, Adr1, Swi5, Ste12, Mcm1, Yap1, Ace1, Ppr1, Arg81, Lac9, Qa1F, VP16, or a mammalian nuclear receptor.

19. The yeast cell of claim 15 wherein at least one of the heterologous fusion proteins is expressed from an autonomously-replicating plasmid.

20. The yeast cell of claim 19 wherein at least one peptide of the peptide binding pair is selected from the group consisting of a cytokine, an interleukin, a hematopoietic growth factor, insulin, an insulin-like growth factor, a growth hormone, prolactin, an interferon, a growth factor, a ligand for G-protein coupled receptors, a ligand for guanylyl cyclase receptors, a ligand for tyrosine phosphatase receptors, and a ligand for tyrosine kinase receptors.

21. The yeast cell of claim 20 wherein the peptide is a growth factor selected from the group consisting of epidermal growth factor, nerve growth factor, leukemia inhibitory factor, fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, tumor necrosis factor, oncostatin M, ciliary neurotrophic factor, erythropoietin, steel factor, placental lactogen, and TGF.

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22. The yeast cell of claim 15 wherein the DNA binding domain is a heterologous transcriptional activation protein DNA-binding domain.

Sub C15 23. The yeast cell of claim 15 wherein the DNA binding protein is selected from the group consisting of a mammalian steroid receptor and bacterial LexA protein.

24. The yeast cell of claim 15 wherein the yeast cell is *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, or *Pichia pastoris*.

25. The yeast cell of claim 24 wherein the yeast cell is *Saccharomyces cerevisiae*.

26. The yeast cell of claim 15 wherein the luciferase gene is a *Renilla* luciferase gene.

27. The yeast cell of claim 15 wherein the luciferase gene is a *Photinus* luciferase gene.

28. The yeast cell of claim 15 wherein the first and second peptides of the peptide binding pair interact through extracellular interaction in their natural environment.

Sub A16 29. A method of detecting the interaction of a first peptide and a second peptide of a peptide binding pair, comprising:

(i) culturing at least one yeast cell, wherein the yeast cell comprises;

a) a nucleotide sequence encoding a first heterologous fusion protein comprising the first

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peptide or a segment thereof joined to a transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising the second peptide or a segment thereof joined to a transcriptional activation protein transcriptional activation domain;

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein;

(ii) incubating a test sample with the yeast cell under conditions suitable to detect the selected phenotype; and

(iii) detecting the level of expression of the luciferase gene.

30. The method of claim 29 wherein the yeast cell further comprises at least one endogenous nucleotide sequence selected from the group consisting of a nucleotide sequence encoding the transcriptional activation protein DNA binding domain, and a nucleotide sequence encoding the transcriptional activation protein transcriptional activation domain wherein at least one of

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the endogenous nucleotide sequences is inactivated by mutation or deletion.

31. The method of claim 29 wherein the peptide binding pair comprises a ligand and a receptor to which the ligand binds.

32. The method of claim 29 wherein the transcriptional activation protein is Gal4, Gcn4, Hap1, Adr1, Swi5, Ste12, Mcm1, Yap1, Ace1, Ppr1, Arg81, Lac9, Qa1F, VP16, or a mammalian nuclear receptor.

33. The method of claim 29 wherein at least one of the heterologous fusion proteins is expressed from an autonomously-replicating plasmid.

34. The method of claim 33 wherein at least one peptide of the peptide binding pair is selected from the group consisting of a cytokine, an interleukin, a hematopoietic growth factor, insulin, an insulin-like growth factor, a growth hormone, prolactin, an interferon, a growth factor, a ligand for G-protein coupled receptors, a ligand for guanylyl cyclase receptors, a ligand for tyrosine phosphatase receptors, and a ligand for tyrosine kinase receptors.

35. The method of claim 34 wherein the peptide is a growth factor selected from the group consisting of epidermal growth factor, nerve growth factor, leukemia inhibitory factor, fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, tumor necrosis factor, oncostatin M, ciliary neurotrophic factor, erythropoietin, steel factor, placental lactogen, and TGF.

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36. The method of claim 29 wherein the DNA binding domain is a heterologous transcriptional activation protein DNA-binding domain.

37. The method of claim 36 wherein the DNA binding protein is selected from the group consisting of a mammalian steroid receptor and bacterial LexA protein.

38. The method of claim 29, wherein the yeast cell is *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, or *Pichia pastoris*.

39. The method of claim 37, wherein the yeast cell is *Saccharomyces cerevisiae*.

40. The method of claim 29 wherein the luciferase gene is a *Renilla* luciferase gene.

41. The method of claim 29, wherein the luciferase gene is a *Photinus* luciferase gene.

42. The method of claim 29, wherein the first and second peptides of the peptide binding pair interact through extracellular interaction in their natural environment.

43. A method for determining whether a test sample interacts with a first or second peptide of a peptide binding pair, comprising:

(i) culturing at least one first yeast cell, wherein the first yeast cell comprises;

a) a nucleotide sequence encoding a first heterologous fusion protein comprising the first

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peptide or a segment thereof joined to a transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising the second peptide or a segment thereof joined to a transcriptional activation protein transcriptional activation domain;

wherein the nucleotide sequence encoding the first heterologous fusion protein is present in an effective copy number of at least 5 copies per yeast cell and the nucleotide sequence encoding the second heterologous fusion protein is present at a copy number of 1 or 2 per yeast cell;

and

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein;

(ii) culturing at least one second yeast cell, wherein the second yeast cell comprises;

a) a nucleotide sequence encoding a first heterologous fusion protein comprising the first peptide or a segment thereof joined to a

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transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising the second peptide or a segment thereof joined to a transcriptional activation protein transcriptional activation domain;

wherein the nucleotide sequence encoding the second heterologous fusion protein is present in an effective copy number of at least 5 copies per yeast cell and the nucleotide sequence encoding the first heterologous fusion protein is present at a copy number of 1 or 2 per yeast cell;

and

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein;

(iii) incubating a test sample with the first and second yeast cells under conditions suitable to detect luciferase activity;

(iv) detecting the presence or absence of luciferase activity produced by the first and second yeast cells; and

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(v) comparing the luciferase activity of the first and second yeast cells, wherein a change in the luciferase activity in one of the yeast cells indicates that the test sample binds to the heterogeneous fusion protein encoded by the nucleotide sequence present at a copy number of 1 or 2 in that yeast cell exhibiting luciferase activity, thereby affecting the binding interaction of the peptide binding pair.

44. The method of claim 43 wherein the yeast cell further comprises at least one endogenous nucleotide sequence selected from the group consisting of a nucleotide sequence encoding the transcriptional activation protein DNA binding domain, and a nucleotide sequence encoding the transcriptional activation protein transcriptional activation domain wherein at least one of the endogenous nucleotide sequences is inactivated by reconstitution or deletion.

45. The method of claim 43 wherein the peptide binding pair comprises a ligand and a receptor for the ligand.

46. The method of claim 43 wherein the transcriptional activation protein is Gal4, Gcn4, Hap1, Adr1, Swi5, Ste12, Mcm1, Yap1, Ace1, Ppr1, Arg81, Lac9, Qa1F, VP16, or a mammalian nuclear receptor.

47. The method of claim 43 wherein at least one of the heterologous fusion proteins is expressed from an autonomously-replicating plasmid.

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48. The method of claim 47 wherein at least one peptide of the peptide binding pair is selected from the group consisting of a cytokine, an interleukin, a hematopoietic growth factor, insulin, an insulin-like growth factor, a growth hormone, prolactin, an interferon, a growth factor, a ligand for G-protein coupled receptors, a ligand for guanylyl cyclase receptors, a ligand for tyrosine phosphatase receptors, and a ligand for tyrosine kinase receptors.

49. The method of claim 48 wherein the peptide is a growth factor selected from the group consisting of epidermal growth factor, nerve growth factor, leukemia inhibitory factor, fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, tumor necrosis factor, oncostatin M, ciliary neurotrophic factor, erythropoietin, steel factor, placental lactogen, and TGF.

50. The method of claim 43 wherein the DNA binding domain is a heterologous transcriptional activation protein DNA-binding domain.

51. The method of claim 50 wherein the DNA binding protein is selected from the group consisting of a mammalian steroid receptor and bacterial LexA protein.

52. The method of claim 43 wherein the yeast cell comprises:

a) a nucleotide sequence encoding a first heterologous fusion protein comprising a first peptide of a peptide binding pair that bind

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through extracellular interaction in their natural environment, or a segment thereof, joined to a transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising a second peptide of the binding pair, or a segment thereof, joined to a transcriptional activation protein transcriptional activation domain;

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein.

53. The method of claim 43 wherein the yeast cell is *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, or *Pichia pastoris*.

54. The method of claim 53 wherein the yeast cell is *Saccharomyces cerevisiae*.

55. The method of claim 43 wherein the luciferase gene is a *Renilla* luciferase gene.

56. The method of claim 43 wherein the luciferase gene is a *Photinus* luciferase gene.

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57. The method of claim 43 wherein the first and second peptides of the peptide binding pair interact through extracellular interaction in their natural environment.

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58. A method of simultaneously detecting the interaction of two different peptide binding pairs, wherein the first peptide binding pair comprises a first peptide and a second peptide, and wherein the second peptide binding pair comprises a third peptide and a fourth peptide, comprising:

(i) culturing at least one yeast cell, wherein the yeast cell comprises;

a) a nucleotide sequence encoding a first heterologous fusion protein comprising the first peptide or a segment thereof joined to a DNA binding domain of a first transcriptional activation protein;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising the second peptide or segment thereof joined to a transcriptional activation domain of the first transcriptional activation protein;

c) a nucleotide sequence encoding a third heterologous fusion protein comprising the third peptide or segment thereof joined to a DNA binding domain of a second transcriptional activation protein;

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d) a nucleotide sequence encoding a fourth heterologous fusion protein comprising the fourth peptide or a segment thereof joined to a transcriptional activation domain of the second transcriptional activation protein;

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes the first transcriptional activation protein, and binding of the third peptide or segment thereof and the fourth peptide or segment thereof reconstitutes the second transcriptional activation protein;

c) a first luciferase gene activated under positive transcriptional control of the first reconstituted transcriptional activation protein;

d) a second luciferase gene activated under positive transcriptional control of the second reconstituted transcriptional activation protein; and

(ii) incubating at least one test sample with the yeast cell under conditions suitable to detect luciferase activity; and

(iii) detecting the level of expression of the first and second luciferase genes.

59. The method of claim 58 wherein the yeast cell further comprises at least one endogenous nucleotide sequence selected from the group consisting of a nucleotide sequence encoding the

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transcriptional activation protein DNA binding domain, and a nucleotide sequence encoding the transcriptional activation protein transcriptional activation domain wherein at least one of the endogenous nucleotide sequences is inactivated by mutation or deletion.

60. The method of claim 58 wherein at least one of the peptide binding pairs comprises a ligand and a receptor to which the ligand binds.

61. The method of claim 58 wherein the first or second transcriptional activation protein is Gal4, Gcn4, Hap1, Adr1, Swi5, Ste12, Mcm1, Yap1, Ace1, Ppr1, Arg81, Lac9, Qa1F, VP16, or a mammalian nuclear receptor.

62. The method of claim 58 wherein at least one of the heterologous fusion proteins is expressed from an autonomously-replicating plasmid.

63. The method of claim 62 wherein at least one peptide of the peptide binding pairs is selected from the group consisting of a cytokine, an interleukin, a hematopoietic growth factor, insulin, an insulin-like growth factor, a growth hormone, prolactin, an interferon, a growth factor, a ligand for G-protein coupled receptors, a ligand for guanylyl cyclase receptors, a ligand for tyrosine phosphatase receptors, and a ligand for tyrosine kinase receptors.

64. The method of claim 62 wherein the peptide is a growth factor selected from the group consisting of epidermal growth factor, nerve growth factor, leukemia inhibitory factor,

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fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, tumor necrosis factor, oncostatin M, ciliary neurotrophic factor, erythropoietin, steel factor, placental lactogen, and TGF.

65. The method of claim 58 wherein the DNA binding domain is a heterologous transcriptional activation protein DNA-binding domain.

66. The method of claim 65 wherein the DNA binding protein is selected from the group consisting of a mammalian steroid receptor and bacterial LexA protein.

67. The method of claim 58, wherein the yeast cell is *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, or *Pichia pastoris*.

68. The method of claim 67, wherein the yeast cell is *Saccharomyces cerevisiae*.

69. The method of claim 58 wherein the first and second peptides of the peptide binding pair interact through extracellular interaction in their natural environment.

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